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**BEFORE THE
SUBCOMMITTEE ON HEALTH
COMMITTEE ON ENERGY AND COMMERCE
UNITED STATES HOUSE OF REPRESENTATIVES**

THE THREAT OF AND PLANNING FOR PANDEMIC FLU

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Mr. Chairman and Members of the Subcommittee, I am Dr. Dominick Iacuzio, Medical Director at Hoffmann-La Roche Inc. ("Roche"), a research-based pharmaceutical company. Since joining Roche, I have been the medical officer responsible for Tamiflu® (oseltamivir phosphate), the world's first oral medication effective against the type A and B strains of the influenza virus. Prior to joining Roche, I worked at the National Institute of Allergy and Infectious Diseases, National Institutes of Health, where I served as the Respiratory Disease Branch's principal technical advisor for the Influenza Program. I am grateful for this opportunity to discuss with you the role of antiviral drugs in pandemic influenza preparedness and response, and I commend the Subcommittee for its efforts to protect the American people against this very real public health threat.

THE PANDEMIC INFLUENZA THREAT

Every year, seasonal influenza causes an average of 36,000 deaths and 114,000 hospitalizations.¹ In addition to the annual influenza seasons, three influenza pandemics took place during the 20th century. In 1918, approximately 500,000 people died from the so-called "Spanish

¹ Department of Health and Human Services, *Draft Pandemic Influenza Response and Preparedness Plan, Core Document*, 14 (Aug. 2004), available at <http://www.hhs.gov/nvpo/pandemicplan/finalpandemiccore.pdf>.

Flu,” and up to 50 million may have died worldwide. The 1957-58 “Asian flu” killed 70,000 Americans, and the 1968-69 “Hong Kong flu” caused over 34,000 deaths in this country.²

An influenza pandemic occurs when an existing influenza strain mutates. The emergence of such a new viral strain, the lack of previous exposure and immunity to the virus, and the lack of a vaccine that can protect against the new strain can ignite a global influenza epidemic, *i.e.*, a pandemic. It has been 36 years since the last influenza pandemic, thanks in large part to the development of influenza vaccinations, as well as methods to predict influenza strains and redesign vaccines annually to include the strains predicted to affect the population in a given year.

However, it appears that the factors associated with a pandemic are now moving into place. First, we have a highly pathogenic strain of avian influenza circulating widely in Asia. Second, this avian strain appears to be increasingly capable of causing deadly disease in humans and animals. In fact, the avian virus has been fatal in approximately 60 percent of people infected by it.³ While efficient human-to-human transmission of the virus – the final barrier to an influenza pandemic – has yet to occur, it is possible – if not probable – that persons harboring both human and avian influenza viruses could become “mixing vessels” from which a new virus emerges that is easily transmitted among humans. Indeed, a recent World Health Organization (WHO) assessment noted that new epidemiological findings in Asia indicate that the virus may be becoming more capable of human-to-human transmission.⁴

Make no mistake: should an influenza pandemic occur, the threat to the U.S. public would be great. In its draft *Pandemic Influenza Preparedness and Response Plan* (Plan), the U.S. Department of

² Centers for Disease Control and Prevention, *Fact Sheet: Information About Influenza Pandemics* (March 8, 2005).

³ World Health Organization, *Cumulative Number of Confirmed Human Cases of Avian Influenza A/ (H5N1) Reported to WHO* (May 19, 2005), *available at* http://www.who.int/csr/disease/avian_influenza/country/cases_table_2005_05_19/en/print.html.

⁴ World Health Organization, *Inter-country Consultation, Influenza A/H5N1 in Humans in Asia* (May 6-7, 2005).

Health and Human Services (HHS) recognizes an influenza pandemic as having “a greater potential to cause rapid increases in death and illness than virtually any other natural health threat.”⁵ Health experts estimate that if the virus is passed efficiently between humans, avian flu could result in a pandemic causing over 50 million deaths worldwide.⁶ Studies cited recently by the Centers for Disease Control and Prevention (CDC) estimate that, without vaccines or drugs, a “medium level” pandemic would kill between 89,000 and 207,000 Americans, and sicken another 20 to 47 million – causing up to 42 million outpatient visits and 734,000 hospitalizations.⁷ In fact, according to the Department of Homeland Security, the potential consequences of even a limited influenza pandemic could result in deaths, hospitalizations and economic disruption far in excess of most terror attack scenarios.⁸ In addition to the human toll, the economic cost of such a pandemic has been estimated at \$71 to \$167 billion.⁹ Without a doubt, planning for such a global health crisis must be a major public health priority.

Both the HHS Plan and the WHO *Global Influenza Preparedness Plan* emphasize that adequately addressing the threat of a pandemic influenza outbreak will require availability of both an influenza vaccine and antiviral drugs.¹⁰ If available, vaccines, which typically are administered before

⁵ Department of Health and Human Services, *Draft Pandemic Influenza Response and Preparedness Plan, Executive Summary* 3, (Aug. 2004), available at <http://www.hhs.gov/nvpo/pandemicplan>.

⁶ World Health Organization, *Estimating the Impact of the Next Influenza Pandemic: Enhancing Preparedness* (Dec. 8, 2004), available at http://www.who.int/csr/disease/influenza/preparedness2004_12_08/en/index.html.

⁷ Centers for Disease Control and Prevention, *Influenza Pandemic Fact Sheet* (Mar. 8, 2005), available at <http://www.cdc.gov/flu/avian/gen-info/pandemics.htm>.

⁸ *15 Nightmares for Disaster Planning*, N.Y. Times (March 16, 2005).

⁹ CDC, *Influenza Pandemic Fact Sheet*.

¹⁰ Department of Health and Human Services, *Draft Pandemic Influenza Response and Preparedness Plan, Core Document* 23 (Aug. 2004), available at <http://www.hhs.gov/nvpo/pandemicplan/finalpandemiccore.pdf>; World Health Organization, *WHO Global Influenza Preparedness Plan* 13 (2005), available at http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_GIP_2005_5.pdf.

an outbreak of influenza, can provide an effective defense against developing seasonal or pandemic influenza, as well as in slowing transmission among humans.

However, vaccines have important limitations. First, accurately predicting the specific viral strain or strains that ultimately may cause an influenza pandemic cannot be assured. Consequently, effective vaccines may not be available at the time a pandemic outbreak is first detected. Second, the propensity of viruses to mutate can lead to the rapid generation of new strains. Thus, there is a possibility that a vaccine effective against the viral strain accountable for the outbreak may be impotent against the virus' mutated progeny. This is one reason why unique vaccines to guard against seasonal influenza must be produced, licensed, and distributed each year, and thus, cannot be stockpiled for use against multiple outbreaks. Finally, given the pace of an outbreak of pandemic influenza, initial reliance on vaccines may not be feasible. For example, the WHO estimates it will take six to nine months to develop a vaccine effective against the circulating pandemic virus strain.¹¹ Of course, producing and distributing the vaccine on a large scale also will take considerable time, and a vaccine, once administered, may take several weeks to trigger immunity, or require multiple administrations.

For all of these reasons, HHS and the WHO have recommended that efforts to prepare for an influenza pandemic not rely on vaccines alone. As stated in a recent WHO report, “[p]ending the availability of vaccines, antiviral agents will be the principal medical intervention for reducing morbidity and mortality, which becomes the most important priority once a pandemic is underway.”¹² Notably, certain antiviral drugs can be used either to treat the flu or as a prophylactic to prevent those at risk from becoming infected. Recently published models suggest that an

¹¹ World Health Organization (WHO) Global Influenza Preparedness Plan: The Role of WHO and Recommendations for National Measures Before and During Pandemics (Apr. 2005), *available at* http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_EDC_99_1/en/print.html.

¹² World Health Organization, *Avian Influenza: Assessing the Pandemic Threat* (Jan. 2005), *available at* <http://www.who.int/csr/disease/influenza/H5N1-9reduit.pdf>.

influenza pandemic could be contained if 80 percent of those exposed to the virus used targeted antiviral drugs prophylactically.¹³

Finally, antivirals have four additional characteristics that warrant their inclusion in any influenza pandemic plan: (1) antivirals have a long shelf-life, permitting them to be stockpiled for several years, and thus immediately available when an outbreak occurs; (2) antiviral drugs begin to work immediately after they are administered; (3) certain antivirals work against multiple types of influenza; and (4) utilization of antivirals does not interfere with immunologic response.

THE ROLE OF TAMIFLU® IN AN INFLUENZA PANDEMIC

Roche's Tamiflu® (oseltamivir phosphate) is the leading prescription oral antiviral drug. Tamiflu® was approved by the Food and Drug Administration (FDA) in 1999 for the treatment of type A and B influenza. Specifically, Tamiflu®, a neuraminidase inhibitor, works by attacking the influenza virus and its ability to replicate, rather than simply addressing influenza symptoms. Tamiflu® is indicated for treatment of patients one year and older, and, if taken within forty-eight hours of the onset of symptoms, can help patients recover from the flu faster. As a prophylactic, an indication approved in 2000, Tamiflu® is labeled for use by adults and adolescents 13 years of age and older, although data on children one year of age and older have recently been submitted to FDA for review. Tamiflu® has a low likelihood of clinically significant drug interactions and is generally well-tolerated, with nausea and vomiting being the most frequently reported adverse events. Tamiflu® is available in both capsule and pediatric suspension form.

As CDC Director Dr. Julie Gerberding informed this Subcommittee in a November 2004 hearing, Tamiflu® “is the only antiviral drug known to be effective against avian influenza.”¹⁴ The

¹³ N.M. Ferguson et al., *A Population-Dynamic Model for Evaluating the Potential Spread of Drug-Resistant Influenza Virus Infections During Community-Based Use of Antivirals*, 51 *Journal of Antimicrobial Chemotherapy* 977 (2003); I.M. Longini et al., *Containing Pandemic Influenza with Antiviral Agents*, 159 *Am. J. Epidemiology* 623 (2004).

¹⁴ *Flu Vaccine and Protecting High-Risk Individuals: Hearing Before the Subcomm. on Health of the House Comm. on Energy & Commerce* 108th Cong. (Nov. 18, 2004) (Statement of Dr. Julie Gerberding).

efficacy of Tamiflu® against avian influenza has been demonstrated in animal studies by leading researchers, *in vitro* data, and practical experience during an avian influenza outbreak in the Netherlands.¹⁵ Accordingly, the WHO has recommended use of Tamiflu® in those potentially exposed to avian flu in Asia.¹⁶ Additionally, while a possibility exists for an influenza virus to emerge with decreased sensitivity to any antiviral drug, the Tamiflu®-resistant viruses isolated in humans to date do not appear to be effectively transmissible.¹⁷

For the prevention of influenza in those 13 years or older, Tamiflu® is administered following close contact with an infected individual who demonstrates characteristic symptoms of influenza, and based on knowledge that influenza is circulating in the area for 10 days, or up to six weeks for seasonal prophylaxis. The approved dose and duration of treatment – 75mg twice daily for five days – is expected to represent the minimum required for the management of an influenza pandemic. To ensure Tamiflu® remains effective against the influenza virus, Roche does not recommend strategies which may utilize lower doses or shorter duration of therapy compared with the recommended dose.

¹⁵ I.A. Leneva et al., *The Neuraminidase Inhibitor GS4104 (Oseltamivir Phosphate) is Efficacious Against A/Hong Kong/156/97 (H5N1) and A/Hong Kong/1074/99 (H9N2) Influenza Viruses*, 48 Antiviral Res 101 (2000).

¹⁶ World Health Organization, *WHO Interim Guidelines for Health Monitoring of Persons Involved in Culling of Animals Potentially Infected with Highly Pathogenic Avian Influenza Viruses* (Mar. 22, 2004), available at http://www.wpro.who.int/avian_flu/docs/Health_monitor_person.asp.

¹⁷ Data collected from patients treated with Tamiflu®, at its approved dose and for the approved treatment duration, demonstrate an overall incidence of resistant virus of only 0.4 percent in adults and four percent in children aged one to 12. All of the resistant virus strains were found unlikely to spread within a community, even under conditions of widespread Tamiflu® use for both treatment and prevention of influenza. N. Roberts, *Treatment of Influenza with Neuraminidase Inhibitors: Virological Implications*, 356 Philosophical Transactions of the Royal Society 1895 (2001).

ALTHOUGH ROCHE IS TAKING STEPS TO INCREASE TAMIFLU® PRODUCTION, THE U.S. GOVERNMENT MUST MAKE CONTRACTUAL STOCKPILE COMMITMENTS TO ENSURE A ROBUST U.S. ANTIVIRAL DRUG SUPPLY

As noted, both HHS and the WHO include stockpiling of antiviral drugs as a central component of their developing plans for influenza pandemic preparedness. Both the Infectious Diseases Society of America (IDSA) and the WHO have recently acknowledged that Tamiflu®, in particular, is uniquely suited to pandemic stockpiling, for several reasons: (1) its efficacy against influenza types A and B; (2) the absence of a known Tamiflu®-resistant virus transmissible in humans; and (3) the product's five-year shelf life.

It is imperative that Tamiflu® be stockpiled in advance of the outbreak of a pandemic because inherent complexities in production severely limit capacity to rapidly meet large-scale, unanticipated demand. The manufacturing process for Tamiflu® is complex, and takes 8-12 months from raw materials to finished product. The process involves many intermediate steps, including a unique starting material, and a potentially explosive production step that can be carried out only in specialized and costly facilities. Given these complexities, significant lead time is needed to increase production capacity and build stockpiles of the quantity required for an influenza pandemic.

Historically, Roche has produced enough Tamiflu® to meet the seasonal influenza demand. For example, just over one million prescriptions for Tamiflu® were written in 2003 in the United States, while preceding years averaged 600,000 to 700,000 prescriptions. In contrast, the IDSA has recommended that the government stockpile enough antiviral drugs to treat up to 50 percent of the U.S. population.¹⁸

¹⁸ World Health Organization, *Governments in a Dilemma Over Bird Flu: Uncertainty Over the Risk Posed by Bird Flu to Human Health Has Left Policymakers in a Dilemma* (May 1, 2005), available at

Despite the obstacles I have described, the company doubled production capacity at our European facility from 2003 to 2004, and we are doing so again during 2005. Roche plans additional expansion of production capacity for Tamiflu® in 2006. Most importantly, early in our discussions HHS made several requests to Roche, all of which we have fulfilled. First, Roche has developed a U.S.-based supply chain. When that supply chain is launched later this year, total Tamiflu® active pharmaceutical ingredient and capsule production capacity will have increased globally by nearly eight-fold over production capacity in 2003. Second, Roche developed special U.S. packaging for stockpiled Tamiflu in order to extend dating and ease distribution and administration. Roche undertook these efforts in good faith and at great economic risk. Moreover, Roche is developing a synthetic process for manufacturing the chemical used in the initial production step, which will ultimately reduce reliance on natural sources.

Roche has received and is filling – on schedule -- pandemic stockpile orders for Tamiflu® from 25 countries worldwide. Discussions are underway for the U.S. government to purchase for its stockpile significantly greater amounts of Tamiflu® for this year and beyond. However, HHS stockpile purchases to date total approximately 2.3 million courses of treatment, or enough to treat less than one percent of the U.S. population. We have also received a non-binding letter of intent for HHS to purchase an additional three million courses of treatment, or enough to cover under two percent of the population. In contrast, countries such as the United Kingdom, France, Finland, Norway, Switzerland and New Zealand are ordering enough Tamiflu® to cover between 20 to 40 percent of their populations.

<http://www.who.int/bulletin/volumes/83/5/infocus0505/en/index1.html>; Infectious Diseases Society of America *IDSA's Principles For Action Needed to Prepare the U.S. to Effectively Respond to Interpandemic/ Pandemic Influenza* (Mar. 10, 2005), available at <http://www.idsociety.org/Template.cfm?Section=Search&CONTENTID=10445&TEMPLATE=/ContentManagement/ContentDisplay.cfm>.

Unfortunately, given the complexities I have described, any government that does not stockpile sufficient quantities of Tamiflu® in advance cannot be assured an adequate supply at the outbreak of an influenza pandemic. We are greatly concerned that with the continually increasing global demand for Tamiflu®, and in the absence of a long-term U.S. commitment to stockpile the product, U.S.-manufactured Tamiflu® may have to be exported to countries with committed orders. While Roche commends HHS for its efforts to date, we cannot emphasize enough the immediate need for the United States government to make the contractual commitments necessary to ensure that an adequate stockpile is developed to meet the looming pandemic threat.

Alerted to the pandemic threat, governments now have an unprecedented opportunity to attempt to minimize the catastrophic loss of life, debilitating illness, and enormous economic costs that a pandemic could wreak on the United States and the world. If I can leave you with three messages from my testimony today, they are the following. First, there is a consensus by leading global health authorities that Tamiflu® is effective and an important tool in pandemic preparedness and response. Second, other nations are currently well ahead of the United States in Tamiflu® stockpiling. Finally, there are important practical constraints on the production of Tamiflu® that make immediate U.S. contractual commitments for future pandemic supplies a necessity.

We at Roche want to continue to work closely with this Subcommittee, HHS, and governments around the world to assist in ensuring our pandemic preparedness. On behalf of Roche, thank you for highlighting the importance of this critical issue, and I will be pleased to answer any questions you may have.